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CASE REPORT

A Case of Thymoma, Myasthenia Gravis and Disseminated Tuberculosis

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THIS case is reported because of the interesting combination of a thymoma, myasthenia gravis and tuberculosis; and because the response to therapy of all three disorders was excellent. It is interesting that as far back as 1901, Weigert[2] first recorded a case of myasthenia gravis with a thymic growth. We did not find any reference in the literature in which tuberculosis was associated with either a thymoma or myasthenia gravis, and we assume that the simultaneous occurrence in the case presented is a matter of coincidence. In addition, this case clearly emphasizes the importance of diagnostic vigilance even in the presence of a disease which apparently accounts for the total clinical picture.

The patient, G.B., a 28-year-old man, was first seen in September 1958 after he had been admitted to hospital for investigation. He reported that he had been perfectly well until three weeks previously, when he first noticed increasing difficulty in eating, swallowing and speaking. He felt weak and tired, and had difficulty in breathing and coughing properly. He also complained of food regurgitating through his nose. The patient gave no history of any previous symptoms of this kind, and there was nothing remarkable in his previous medical history or in his family history.

This man had been referred initially for a psychiatric examination, and a provisional diagnosis had been made of "hysterical reaction in a person of somewhat limited intelligence". Because of the complaint of dysphagia, a barium meal was performed; this showed no intrinsic abnormality of the esophagus but clearly demonstrated a large anterior mediastinal tumour associated with some degree of atelectasis of the left lower lobe. The patient was then seen by an ear, nose and throat surgeon, who suspected myasthenia gravis associated with a tumour of the thymus. This diagnosis was confirmed when the patient's recovery from muscle weakness was demonstrated following a test injection of 1.5 mg. of neostigmine (Prostigmine). Further opinions were obtained, and the advisability of thoracotomy was discussed. However, his general condition was deteriorating rapidly; he was now having great difficulty in breathing and coughing, and was unable to talk except after the adminstration of neostigmine. Even then his voice soon faded away if he was asked to count up to 20. All the muscles of the face were very weak, but there was no ptosis, diplopia, or any evidence of involvement of the ocular muscles. A second chest radiograph (Fig. 1), taken only 10 days after the first, showed several discrete, rounded shadows in the left lung field, which were thought to be probably pleural deposits. Now there was also evidence of a pleural effusion at the left lung base, and aspiration showed this to be blood-stained. Because of this, the proposed thoracotomy was abandoned. Although there was no histologic confirmation, the diagnosis of malignant thymoma and acute myasthenia gravis seemed certain on clinical and radiologic grounds. Treatment by means of radiotherapy to the mediastinal mass was therefore commenced.

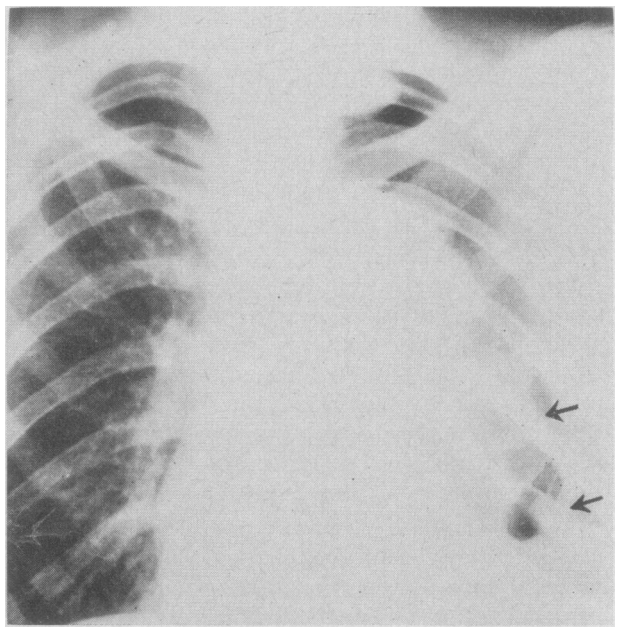

Fig. 1.—Initial radiograph, before radiotherapy, showing left hilar mass and rounded densities in left lower lung field.

X-radiation generated at 220 kilovolts with a half value layer of 1.6 mm. of copper was used. The whole of the mediastinum and left lung was treated in one block, using large parallel opposing fields measuring 28 x 20 cm. The focus-skin distance was 85 cm. The total minimum tissue dose given was 2800 r over a period of five weeks. The "incident" dose measured with full back-scatter was 3110 r, and the estimated maximum skin dose (incident dose plus exit dose) was 3500 r.

During the period of radiation, he continued to look ill and wasted, but the symptoms attributed to myasthenia gravis steadily improved. On the last day of radiation treatment he still required pyridostigmine (Mestinon) in a dose of three 60-mg. tablets every

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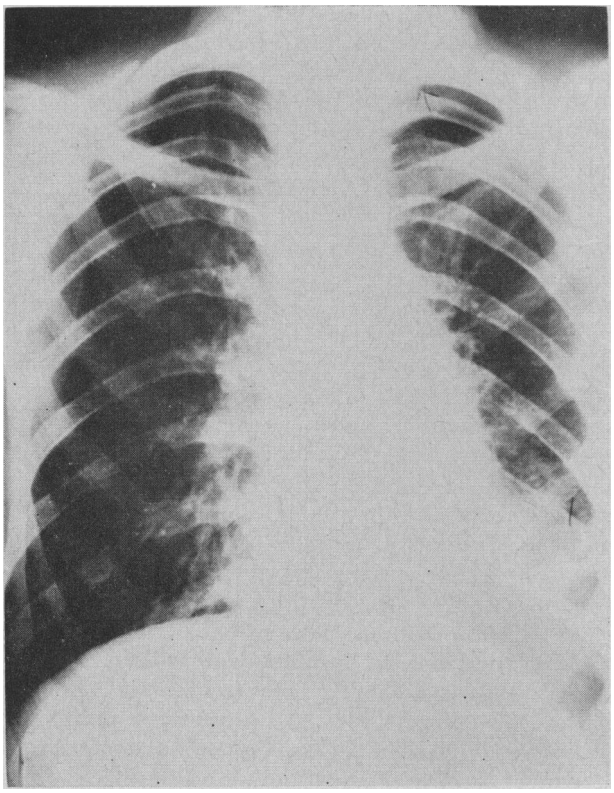

Fig. 2.—Radiograph of chest after radiotherapy was administered, showing only residual involvement of the left lower lobe.

four hours, but he now required injections of neostigmine (2.5 mg. subcutaneously) only two or three times daily before meals; previously he had required at least six injections daily. His speech and the strength of his cough greatly improved. The patient no longer experienced regurgitation of food through the nose, and he could now swallow tablets without having them crushed.

Serial chest radiographs showed that the disease was markedly radiosensitive. Halfway through the course of radiation, it was observed that the mediastinal mass was half its original size, and the discrete rounded shadows were now almost invisible. A few days before radiation therapy was completed, his chest films were virtually normal.

The radiation of this large volume of tissue was well tolerated, and there was no depression of the leukocyte count, which remained between 10,000 and 15,000 per c.mm. The skin over the treated areas showed a dusky erythema at the end of treatment, but this did not cause him any discomfort. Because of the satisfactory clinical and radiological response and the risk of producing radiation pneumonitis if such a large volume of tissue were exposed to higher dose, it was decided to discontinue radiation therapy at the dosage of 2800 r.

The patient improved sufficiently to be discharged to his home two weeks after the completion of radiotherapy, but 10 days later he had to be readmitted to hospital because of fever, shortness of breath and cough. A chest radiograph (Fig. 2) suggested the presence of pneumonia in the left lower lobe.

The condition appeared to respond to penicillin, and the residual symptoms of myasthenia gravis were controlled by the administration of pyridostigmine by mouth without intramuscular injections of neostigmine.

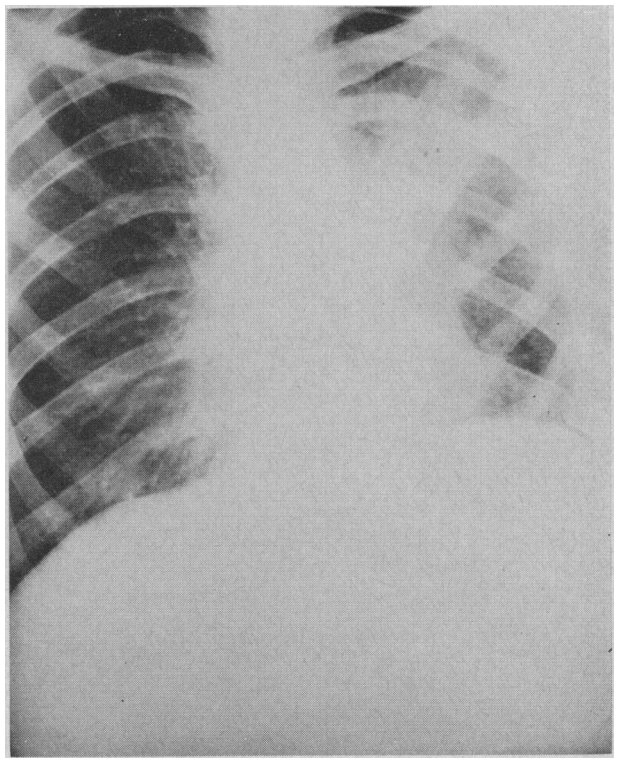

Fig. 3.—This radiograph shows new infiltration of the left upper lobe that occurred after the initial response to therapy. This was tuberculous in origin.

The patient's appetite improved and he began to regain weight.

A chest radiograph now showed a clearing at the left lung base, but there was a new shadow infiltrating outward from the left hilar region. It was thought at first that this change might be due to radiation effect and that its presence did not call for any action other than observation. Again the patient was well enough to be discharged from hospital.

One month later he was readmitted to hospital with a high fever and pain in the left chest. His weight gain had been maintained. The myasthenia was now in complete remission, and he did not require any treatment for it. A chest radiograph (Fig. 3), however, revealed that the infiltration previously seen in the left hilar region had extended into almost the whole of the left upper lung. There was no radiologic evidence of recurrence of the anterior mediastinal thymic mass. It was thought that the patient was suffering from attacks of pneumonia occurring on a background of radiation change and early pulmonary fibrosis. However, he continued to run a high temperature which did not respond to antibiotics, and within a week he developed moderately large discrete lymph nodes on both sides of the neck. These were rubbery in consistency and were very much like the mobile nodes characteristic of Hodgkin's disease. Biopsy of one of these nodes was immediately performed and, to our surprise, this showed vast numbers of acid-fast bacilli, together with a histologic picture of a nonreactive tuberculosis. The sputum also now contained tubercle bacilli, and the diagnosis of tuberculosis was later confirmed by culture. He was transferred to a local sanatorium and was given streptomycin, P.A.S. and isoniazid. At the beginning of this treatment, a chest radiograph showed evidence of extensive changes in both lungs, especially the left,

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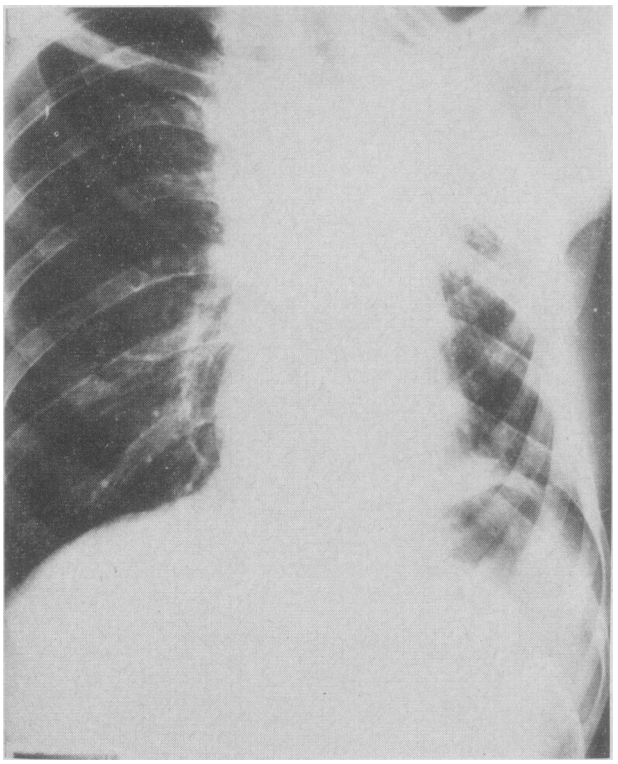

Fig. 4.—A later radiograph after the patient's clinical recovery, showing healed tuberculosis and radiation fibrosis in the left upper lobe.

which were believed to be due to tuberculosis. Gradually his general condition, which was extremely bad for a time, improved. In April 1959, six weeks after transfer to the sanatorium, a laparotomy was performed on this patient because of severe abdominal pain, and the liver was found to be studded with small foci of tuberculosis. No evidence of tuberculous peritonitis was seen. His sputum became negative in May 1959, and remained so, and the radiological appearances gradually improved, finally leaving only a shadow in the left upper lung zone. Throughout this time there was only very mild and occasional evidence of myasthenia, manifested by slight difficulty in swallowing. However, this was hard to assess because it was felt that there might be some functional overlay.

After 16 months in the sanatorium, he was discharged, and up to September 1961 (2½ years after radiotherapy) he has shown no sign of relapse. He has gradually regained weight. For a period he had pain in the left arm and shortness of breath on exertion. These transient symptoms and the persistent radiological changes of the left upper lung (Fig. 4) are thought to be due to fibrosis, partly associated with radiation and partly with healed tuberculosis. His blood count and sedimentation rate are normal. He is happier when taking pyridostigmine bromide (Mestinon) tablets, but there is no real evidence of persistent myasthenia. We are inclined to agree with Keynes[4] in his observation that "among those who have undergone complete recovery, are a few individuals who are unable for psychological reasons entirely to give up taking neostigmine".

DISCUSSION

From this patient's history, his physical findings and his response to neostigmine, there is no doubt that he definitely had severe myasthenia gravis. Similarly, there is no question that at a later date he developed disseminated tuberculosis that was first diagnosed by biopsy of a lymph node. The organism was later isolated from his sputum, and still later evidence of this infection was demonstrated in his liver at laparotomy performed at the sanatorium. We believe that the diagnosis of thymoma is justified, in spite of the lack of histologic confirmation, for the following reasons: first, the associated myasthenia gravis; second, the radiological evidence of a tumour in the anterior mediastinum with discrete rounded deposits in the left lung field, and a pleural effusion that was subsequently found to be bloody; third, the dramatic response to radiation with rapid disappearance of the anterior mediastinal mass, the rounded peripheral shadows, and the pleural effusion. This change and the slower, but equally satisfactory, improvement in the symptoms of myasthenia gravis correspond closely to the experience of Williams,[7] who states, "Some tumours are so sensitive that they are no longer visible radiologically after a tumour dose of 1000 to 1500 r . . . recurrences and deposits within the thoracic cage show the same degree of radiosensitivity. The effect on the myasthenia is slower . . . improvement may continue for some weeks after the end of therapy, and after three months normal activity may be restored." Williams sums up this pattern of response as follows: "We are dealing thus with a tumour that shrinks rapidly, and a disordered physiological condition which responds more slowly."

A report from the same centre by Jones *et al.* (1955),[8] and a personal communication (Jones, 1961)[10] describe several similar cases of myasthenia gravis with thymic tumour and pleural deposits. Some have shown a very satisfactory immediate response to radiotherapy, though the ultimate prognosis has been poor, not so much because of recurrence of the thymoma, but because of the reappearance of the symptoms of myasthenia gravis.

A thymoma rarely, if ever, develops distant metastases.[1, 5] It is felt that it spreads by direct extension to surrounding structures, the lung, pleural space, and only rarely below the diaphragm into the liver. The present case confirms this impression. We were dealing with a patient who had evidence of a thymoma and myasthenia gravis and who then developed generalized lymphadenopathy. At the time the lymph node was biopsied we were certainly thinking of the possibility of distant metastases from the thymoma, even though this was unusual; but the lymph node lesion proved to be disseminated tuberculosis. If we had simply assumed that these enlarged lymph nodes in this very sick patient were due to distant metastases and that nothing could be done, this patient would have died within a very short time, and the opportunity of providing effective treatment of the tuberculosis would have been lost. Another important consideration is the fact that when this

patient demonstrated these enlarged peripheral lymph nodes in association with the lung and mediastinal lesions, consideration was given to the use of corticosteroids and nitrogen mustard, but prior to instituting such treatment, the lymph node biopsy was carried out. The unexpected result of this investigation emphasizes the danger of administering specific therapy to patients who appear to have a terminal neoplasm, without investigating them fully. If this patient had been given nitrogen mustard and corticosteroids, it may well have adversely affected the course of the tuberculous process. Therefore, before the use of any potent and potentially hazardous therapeutic regimen, one should attempt whenever possible to obtain pathologic proof of the diagnosis.

This case further illustrates the problem of assessing the symptom of dysphagia in patients with a mediastinal lesion. This patient's major symptom was difficulty in swallowing. However, he had regurgitation through his nose, general weakness, and progressive weakness on talking, indicating that the dysphagia could not be due solely to the mediastinal tumour. This clearly supports the clinical dictum that any patient with difficulty in swallowing should have a therapeutic test with neostigmine before assuming that this symptom is due to causes other than myasthenia.

The case presented also clearly indicates how effective present-day antituberculous therapy can be. This patient was debilitated as a result of myasthenia gravis and a thymoma, and then suffered from the dissemination of tuberculosis involving lymph nodes, lungs, liver, and possibly many other organs, but he still responded well to therapy.

SUMMARY

A patient who had a thymoma with myasthenia gravis, and who later developed disseminated tuberculosis, is presented. This man illustrates the dramatic response of a thymoma with secondary spread and myasthenia gravis to radiation therapy, as well as the excellent response of disseminated tuberculosis to modern-day chemotherapy. More than two and one-half years have elapsed since radiotherapy was administered, and the patient so far shows no recurrence. Additional interesting therapeutic and diagnostic aspects of these conditions have been discussed.

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SHORT COMMUNICATIONS

Desmethylimipramine (G-35020) in the Treatment of Depression: Pilot Study in a General Hospital and Outpatient Setting

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THIS is a report of a preliminary evaluation of the action and efficacy of desmethylimipramine, the purported "active metabolite" of imipramine.

In the course of the past three years the efficacy of imipramine as an antidepressant drug has been reasonably well established.[1-4] Some of the less favourable results seen may reflect the almost inevitable over-enthusiastic response which follows the introduction of any new and effective pharmacologic agent. The new drug tends to be prescribed for a wide range of disorders without careful phenomenologic discrimination or patient selectivity. For example, imipramine has not been found very suitable for depressions associated with schizophrenia or in chronic neurotic depressions with strong masochistic elements, yet it is frequently used in these and other conditions, such as anxiety reactions. Even in more straightforward depressive entities it is not always effective. This may be because of individual idiosyncrasy, but more probably because our knowledge of these conditions—both clinical and biochemical—is still far from complete and the "fields" of depression have not yet been clearly demarcated. However, approaches to this are being made, and it is

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